Grant # AR49555

Center Director: Joel D. Greenspan, Ph.D.

Center Overview

This multidisciplinary SCOR is devoted to the study of the mechanisms of chronic or persistent pain with specialized focus on 1) sex-related factors that influence pain, and 2) painful clinical conditions that demonstrate a high prevalence in women. The Center's research program is diverse, and ranges from molecular studies to systems physiology studies to clinical studies. Our working model is that research on pain has clearly shown that a person's sex is an important factor in determining their perception of, and response to, painful stimulation and pathological pain. Several physiological and psychological mechanisms have been proposed to account for these sex differences, yet many hypotheses remain to be adequately tested. This SCOR would direct its efforts to evaluating physiological models of sex-related pain differences, including the influence of gonadal hormones. Additionally, this Center would evaluate pathophysiological models of chronic pain conditions that are more prevalent in women, focusing on temporomandibular joint disorders (TMD) and the visceral pain associated with conditions such as irritable bowel syndrome (IBS). This Center would facilitate the transfer of basic scientific knowledge to the study of persistent pain in humans, and ultimately to the development of new methods of diagnosing and treating these conditions in the general population.

One clinical and two basic science projects constitute the scientific basis of the application. The two principal objectives of this SCOR are: 1) To elucidate the underlying mechanisms associated with sex differences in persistent pain of deep muscle and visceral origin. Human and animal studies will explore hypothesized physiological mechanisms of sex differences in pain, including opioid receptor expression, peripheral nociceptor sensitivity, CNS sensitization, and CNS ascending/descending modulation, as well as the influence of gonadal steroids on these mechanisms. All three projects address this objective. 2) To explore the neural basis of temporomandibular disorder (TMD) pain, with special emphasis upon sex-related hypotheses. TMD is the major persistent orofacial pain condition of deep tissue origin. It shows a large prevalence in women of childbearing age. The pathophysiology of TMD is poorly understood, but several hypotheses based on sex-related factors have been proposed. Two of the proposed projects (#1and #3) direct efforts explicitly to evaluate such hypotheses.

Principal Investigator: Joel D. Greenspan, Ph.D.

Project 1: CNS Mechanisms for Gender Differences in Pain, and Their Relevance to Temporomandibular Disorder Pain

This project addresses issues relevant to the CNS mechanisms of pain perception in terms of 1) gender differences in healthy individuals, and 2) contributing factors for temporomandibular disorder (TMD) pain. Two CNS mechanisms that influence nociceptive processing and resulting pain -- temporal summation (TS) of pain and diffuse noxious inhibitory control (DNIC) - will be evaluated in a series of human psychophysical experiments.

TS is the increase in perceived pain intensity when noxious stimuli of a constant intensity are delivered at a sufficiently rapid frequency. TS is centrally mediated and reflects transient up-regulation of the dorsal horn nociceptive neurons' excitability in the spinal cord, and potentially higher CNS regions. One study has reported that TS of heat pain is greater in females than in males, suggesting that females may have more hyperexcitable central nociceptive neurons. Similarly, TMD patients have been reported to show higher temporal summation of heat pain than healthy controls, indicating that up-regulated central processing of nociceptive input may constitute an underlying pathophysiological basis of TMD. One purpose of this project is to investigate differences in temporal summation of mechanically evoked pain between healthy females and healthy males, as well as between TMD patients and healthy controls. Both the sensory and the affective dimensions of pain, as well as the frequency-dependent profile of temporal summation of pain will be evaluated. Moreover, it will be determined if there is a significant correlation between temporal summation of pain and measures of clinical pain in TMD patients.

DNIC is the phenomenon in which persistent noxious stimulation evokes an endogenous analgesic system, resulting in a global attenuation of nociceptive signals. Accordingly, subsequent noxious stimulation elsewhere on the body produces less pain than it otherwise would. Several studies indicate that DNIC engages the endogenous opiate system. Given gender differences in the efficacy of exogenous opiates, this project will examine whether DNIC is significantly stronger in men than women. Additionally, endogenous analgesic systems may be attenuated in cases of prolonged pain, thus contributing to the difficulty in managing chronic pain. This project will compare DNIC efficacy in TMD pain patients, and a sex- and age-matched healthy control group, to determine whether there is a significant difference in the evocation of the endogenous analgesic system. Identifying the roles of these two specific nociceptive processing mechanisms in TMD pain would provide focus for the development of appropriately targeted pain relief treatments.

Identifying gender differences in these two nociceptive processing mechanisms could explain, in part, the female prevalence of TMD, and possibly other chronic pain conditions. In addition, establishing such gender differences would highlight the need consider the person's sex in addressing pain treatment in general.

Principal Investigator: Anne Z. Murphy, Ph.D.

Project 2: Sex Differences in Visceral Pain: Influence of Gonadal Steroids

Irritable bowel syndrome (IBS), a common gastrointestinal disorder characterized by abdominal pain and a change in bowel habits, will affect up to 20% of the general population. Epidemiological studies have established that females are 2-5x more likely to suffer from IBS in comparison to males. A defining characteristic of IBS is severe gastrointestinal pain. Surprisingly, while an extensive body of research has been conducted examining the neural mechanisms underlying visceral pain, these studies have been conducted exclusively in males. Thus, it is not known how visceroceptive information is processed within the CNS of females. Similarly, the impact of gonadal steroids on visceral pain is also not known. Behavioral studies in Aim 1 will characterize the sex differences and influence of gonadal steroids on visceral pain. Our preliminary data indicate that there are profound sex differences in the visceral motor reflex, an indicator of visceral pain following noxious colorectal distention. Our data further show that the sexually dimorphic response to noxious visceral stimulation is estrogen dependent. Anatomical studies proposed in Aim 2 will test the hypothesis that sex differences in the organization and activation of the spinoparabrachial circuit provide the anatomical substrate for the dimorphic response to noxious visceral stimulation. Studies using acute somatic stimuli have reported that morphine produces a significantly greater degree of analgesia in males versus females, and our preliminary studies indicate that morphine alleviation of visceral pain is also sexually dimorphic. Studies proposed in Aim 3 will test the hypothesis that morphine produces a significantly greater degree of analgesia in males in comparison to females in a model of visceral pain. Immunocytochemical and molecular studies proposed in Aim 4 will test the hypothesis that opioid receptor expression within the lumbosacral spinal cord is sexually dimorphic. The influence of gonadal steroids on opioid receptor expression will also be examined. Together, these studies will begin to elucidate the neural mechanisms underlying sex differences in visceral pain.

Principal Investigator: Michael S. Gold, Ph.D.

Project 3: Ionic Mechanisms of TMJ Pain

Temporomandibular disorders (TMD) are often associated with debilitating pain. While both men and women may suffer from TMD pain, the vast majority of those seeking medical attention for relief from TMD pain are women, whose pain is likely to be more severe and last longer than that experienced by men. Indeed, over 80% of those seeking medical attention for relief of TMD pain are women. The molecular basis for the gender difference in the expression and revalence of TMD pain remains unknown. However, epidemiological, clinical and experimental evidence suggests that gonadal hormones, in particular estrogen contributes to this difference. Furthermore, there are several lines of evidence to suggest that a target for estrogen that may contribute to gender differences in TMD pain is temporomandibular joint (TMJ). Importantly, estrogen may influence the excitability of TMJ afferents in normal tissue as well as the increase in excitability observed in the presence of inflammation. In normal tissue, voltage-and Ca2+-activated channels present in the plasma membrane of the afferent terminal control afferent excitability. Changes in the biophysical properties, expression and/or distribution of these channels may have a profound impact on afferent excitability, however, little is known about the impact of estrogen on ion channels in sensory neurons. Furthermore, while several mechanisms mediating acute actions of inflammatory mediators on sensory neuron shave been identified, considerably less is known about mechanisms mediating hyperexcitability in the presence of persistent inflammation and virtually nothing is known about the impact of estrogen on these processes. This is particularly true for joint afferents given the dearth of data on the basic membrane properties of these afferents innervating normal tissue. Therefore, we propose to test the following hypotheses:1) that estrogen increases the sensitivity of the TMJ to noxious stimulation and exacerbates inflammation-induced increases in sensitivity; 2) that estrogen influences the excitability of TMJ neurons through a direct action on these neurons; 3) that estrogen-induced changes in the excitability of TMJ afferents reflects a changes in the expression of voltage-and/or Ca2+ activated channels in these neurons; and 4) that estrogen exacerbates inflammation-induced increases in the excitability of TMJ afferents by influencing inflammation-induced changes in the voltage and/or Ca2. activated channels in these neurons. We will test these hypotheses in a series of experiments employing a combination of behavioral, anatomical, electrophysiological and molecular biological techniques on intact male and gonadectomized female rats, as well as gonadectomized female rats receiving estrogen replacement.